DETAILED ACTION

1. This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 for the reason(s) set forth on the attached Notice To Comply With Requirements For Patent Applications Containing Nucleotide Sequence And/Or Amino Acid Sequence Disclosures. In particular, a SEQ ID NO is required for the sequence disclosed on page 11 of the specification under Table 1.

Applicant is advised that for any response to be considered fully responsive said response has to be fully responsive to the sequence compliance requirements.

2. Applicant's amendments and responses filed 2/27/07, 5/6/10 and 7/15/10 are acknowledged and have been entered.

3. Applicant's election with traverse of Group I and species of an HLA-E chimeric molecule replacing all or part of the α2 domain with all or part of the α2 domain of an HLA-G1 molecule in Applicant's amendment and response filed 7/15/10 is acknowledged.

The basis for Applicant's traversal (of record on pages 3-4 of the said amendment and response filed 7/15/10) is that Matsunami is not available as prior art since it was published after the priority date of November 4, 2003 of the present application, that Applicant may in the future amend the claims of the groups to define over any cited reference, and that there exists no undue administrative burden for the Examiner to search and consider claims 1-5 in their entirety.

Applicant's arguments have been fully considered but are not persuasive.

First, for the purpose of prior art rejections, the filing date of the instant claims is deemed to be the filing date of the instant application *of* PCT/JP04/16776, *i.e.,* 11/04/04. The date referred to by Applicant, *i.e.,* 11/4/03, is the filing date of Applicant's foreign priority document JP 2003-374944, for which Applicant has not provided a certified English language translation.

Second, any unspecified future claim amendments are not relevant to the issue under discussion.

Third, the standard for lack of unity in 371 practice is lack of a technical feature that is distinguished over the prior art (*i.e.,* lack of a "special technical feature"), not the "undue administrative burden", alleged by Applicant. The prior Office Action of record mailed on 6/152/10 clearly meets the standard for establishing lack of unity (see item #2 of said prior Office Action). None-the-less, Group II (claim 2) is drawn to a nucleic acid

molecule and Group III (claim 3) reads on a transgenic nonhuman mammal. As such, if undue search and examination burden were the standard, there would be an undue burden placed upon the Examiner by search and examination of all the groups, as Groups I, II and III have different classification (for example, Class 530/subclass 350, Class 536/subclass 23.5 and Class 800/subclass 8, respectively) and search and examination of all the groups would require employing different search queries.

Claim 1 (at part (1)) reads on the elected species.

Upon consideration of the art, examination has been extended to include the species recited in claim 1 at part (2), *i.e.,* a HLA-E chimeric molecule with the signal peptide of HLA-G1 and a portion of the alpha 2 domain of HLA-E replaced with a part of the alpha 2 domain of HLA-G1.

The requirement is still deemed proper and is therefore made FINAL.

Accordingly, claims 4 and 5 (non-elected species of Group I) and claims 2 and 3 (non-elected groups II and III) are withdrawn from further consideration by the Examiner, 37 CFR 1.142(b), as being drawn to non-elected inventions.

Claim 1 is currently being examined.

4. (a) The abstract of the disclosure is objected to because it contains grammatical errors, such as "providing nonhuman mammal cell" and "The HLA-E chimeric molecule of the invention is a peptide reforming all or part of signal peptide region….". Correction is required. See MPEP § 608.01(b).

(b) The disclosure is objected to because of the following informalities: A SEQ ID NO is required for the sequence appearing on page 11. Appropriate correction is required.

5. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

6. Claim 1 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention.

(a) Claim 1 is indefinite in the recitation of "with reformed SP partly reforming the SP of the HLA-G1 molecule" because it is not clear what is meant.

(b) Claim 1 is indefinite in the recitation of "replacing, together with (2), a part of amino acid sequence of the $\alpha 1$ domain and $\alpha 2$ domain" because it is not clear what is

meant, *i.e.,* part (2) of claim 1 refers back to part (1) of claim 1, and part (1) of claim 1 already recites that all or part of the α2 domain is replaced.

7. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. Claim 1 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an HLA-E chimeric molecule that has all of the α2 domain, the latter part of the α2 domain or the first portion of the latter part of the α2 domain replaced with the corresponding domain portion of HLA-G1, and including optionally replacement of HLA-G1 signal sequence (SP), does not reasonably provide enablement for an HLA-E chimeric molecule that has the first portion of the α2 domain or the first portion of the α2 domain and a part of the α1 domain replaced with the corresponding domain portion of HLA-G1. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The specification has not enabled the breadth of the claimed invention because the claims encompass an HLA-E chimeric molecule that can not be expressed on a cell surface.

The state of the art is such that it is unpredictable in the absence of appropriate evidence whether the claimed compositions can be made and/or used.

The disclosed use for the HLA-E chimeric molecule is to express it on the surface of a xenogenic cell in order to suppress NK cytotoxicity against said xenogenic cell for the purpose of xenotransplantation(especially page 2 at the first full paragraph through page 4 at the second full paragraph). The specification further discloses working examples of chimeric HLA-E molecules in which the SP of HLA-G1 replaces the SP of HLA-E, and additionally, the entire α2 region is replaced with that of HLA-G1, or the latter part of the α2 region is replaced with that of HLA-G1 or the fore part of this latter part of the α2 region is replaced with that of HLA-G1 (see Table 1 on page 11).

When the inventors replaced (also with the SP of HLA-G1 replacing the SP of HLA-E) the latter part of α2 domain with the corresponding part of HLA-G1, or when they replaced the α1 domain with the corresponding part of HLA-G1, cell surface expression was not increased over that seen with native HLA-E (see Table 11).

Evidentiary reference Matsunami *et al* (BBRC, 2006, 347: 692-697) teach that when the α1 domain of HLA-E is replaced with that of HLA-G1, there is no cell surface expression of the chimeric HLA-E molecule (especially Figure 1 and page 694 at the first paragraph

of the Results section). Matsunami *et al* also teach the importance of the first portion of the later half of the α2 domain, particularly residue 147 in cell surface expression (see especially second paragraph of results section and Figure 1).

Thus, it is unpredictable if an HLA-E chimeric molecule that has the first portion of the α2 domain, or the first portion of the α2 domain and a part of the α1 domain, replaced with the corresponding domain portion of HLA-G1 can be used for the disclosed purpose of cell surface expression and inhibition of NK cell activity in xenotransplantation.

There is insufficient guidance in the specification as to how to make and/or use instant invention. Undue experimentation would be required of one skilled in the art to practice the instant invention. See In re Wands 8 USPQ2d 1400 (CAFC 1988).

9. For the purpose of prior art rejections, the filing date of the instant claims is deemed to be the filing date of PCT/JP04/16776, *i.e.,* 11/04/04. Applicant has not provided a certified English language translation of Applicant's foreign priority document JP 2003-374944 filed 11/4/03.

10. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

11. Claim 1 is rejected under 35 U.S.C. 102(b) as being anticipated by Strong *et al* (J. Biol. Chem. 2/14/03, 278(7): 5082-5090) as evidenced by an admission in the specification at SEQ ID NO: 13 of the sequence listing and as evidenced by Matsunami *et al* (J. Biochem. 2008, 143: 641-647).

Strong *et al* teach a chimeric HLA-E*0101 molecule that has amino acid residue 107 in the alpha 2 domain replaced with glycine that is found at position 107 in the alpha 2 domain of HLA-G1 (meets the limitation of claim 1, part (1)). Strong *et al* also teach this chimeric molecule fused to the leader sequence of HLA-G1, *i.e.,* to VMAPRTLFL (meets the limitation of claim 1, part (2)) (especially abstract, paragraph spanning columns 1-2 on page 5083, and paragraph spanning columns 1-2 on page 5086).

SEQ ID NO: 13 of the instant specification is the α2 domain of HLA-G1. It has a glycine at position 17, corresponding to amino acid residue 107 of HLA-G1.

Evidentiary reference Matsunami *et al* teach that position 107 of HLA-G1 and of HLA-E resides in the α2 domain (especially Figure 1A).

Although the art reference does not teach that the leader sequence is the signal peptide, it is common in the art that these terms are used synonymously to depict signal peptides.

Furthermore, it is noted that there is no recited sequence in the instant claim 1. The definition of the limitation "reformed SP" (recited in instant claim 1) in the instant specification is found in the paragraph spanning pages 4-5, *i.e.,* "The reformed SP means a sequence of amino acid sequence of SP in which one or two or more amino acids are replaced or deleted, or one or more amino acids are added,". The disclosure at the said paragraph continues to give an example of a reformed SP.
Therefore the claimed chimeric molecule appears to be the same as the chimeric molecule of the prior art absent a showing of differences. Since the Patent Office does not have the facilities for examining and comparing the composition of the instant invention to those of the prior art, the burden is on Applicant to show a distinction between the chimeric molecule of the instant invention and that of the prior art. See In re Best, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977).

12. Claim 1 is rejected under 35 U.S.C. 102(a) as being anticipated by Matsunami *et al* (Transplantation, 78(2), page 157, Abstract O401, July 27, 2004, of record).

Matsunami *et al* teach HLA-E chimeric molecules that have substitutions of portions of HLA-E with portions of HLA-G1: the signal peptide of HLA-G1, and additionally point substitution(s) in the α1 or α2 domains, the signal peptide of HLA-G1 plus the α1 and α2 domains of HLA-G1, or the HLA-G1 signal peptide plus the α2 domain of HLA-G1.

13. No claim is allowed.

14. Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Marianne DiBrino whose telephone number is 571-272-0842. The Examiner can normally be reached on Monday, Tuesday, Thursday and Friday.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Ram Shukla, can be reached on 571-272-0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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/G.R. Ewoldt/
Primary Examiner, Art Unit 1644

Applicant and the assignee of this application are required under 37 CFR 1.105 to provide the following information that the Examiner has determined is reasonably necessary to the examination of this application.

Matsunami *et al* (Transplantation, 78(2), page 157, Abstract O401, July 27, 2004, of record) has been cited by the Examiner supra. The said reference has two authors, Matsunami and Miyagawa, who are also inventors of the instant application. The reference is an "Oral Abstract" published on September 9, 2004.

Said abstract teaches HLA-E chimeric molecules wherein said HLA-E chimeric molecules have substitutions of portions of HLA-E with portions of HLA-G1: the signal peptide of HLA-G1, and additionally point substitution(s) in the α1 and α2 domains, the signal peptide of HLA-G1 plus the α1 and α2 domains of HLA-G1, or the HLA-G1 signal peptide plus the α2 domain of HLA-G1.

In the biological sciences it is customary for scientists to present their work to others at meetings either orally with slides or with an abstract of the material present on the poster being bound and published for dissemination to scientists who could not attend the meeting in person. As such, the presentation or poster presented at the meeting comprises more data than what can be contained in an abstract. Applicant is reminded that as per MPEP 2128.01:

> **>IV. PUBLICLY DISPLAYED DOCUMENTS CAN CONSTITUTE A "PRINTED PUBLICATION" EVEN IF THE DURATION OF DISPLAY IS FOR ONLY A FEW DAYS AND THE DOCUMENTS ARE NOT DISSEMINATED BY COPIES OR INDEXED IN A LIBRARY OR DATABASE**
>
> A publicly displayed document where persons of ordinary skill in the art could see it and are not precluded from copying it can constitute a "printed publication," even if it is not disseminated by the distribution of reproductions or copies and/or indexed in a library or database. As stated in *In re Klopfenstein*, 380 F.3d 1345, 1348, 72 USPQ2d 1117, 1119 (Fed. Cir. 2004), "the key inquiry is whether or not a reference has been made 'publicly accessible.'" Prior to the critical date, a fourteen-slide presentation disclosing the invention was printed and pasted onto poster boards. The printed slide presentation was displayed with no confidentiality restrictions for approximately three cumulative days at two different industry events. 380 F.3d at 1347, 72 USPQ2d at 1118. The court noted that "an entirely oral presentation that includes neither slides nor copies of the presentation is without question not a 'printed publication' for the purposes of 35 U.S.C. § 102(b). Furthermore, a presentation that includes a transient display of slides is likewise not necessarily a 'printed publication.'" 380 F.3d at 1349 n.4, 72 USPQ2d at 1122 n.4. In resolving whether or not a temporarily displayed reference that was neither distributed nor indexed was nonetheless made sufficiently publicly accessible to count as a "printed publication" under 35 U.S.C. 102(b), the court considered the following factors: "the length of time the display was exhibited, the expertise of the target audience, the existence (or lack thereof) of reasonable expectations that the material displayed would not be copied, and the simplicity or ease with which the material displayed could have been copied." 380 F.3d at 1350, 72 USPQ2d at 1120. Upon reviewing the above factors, the court concluded that the display "was sufficiently publicly accessible to count as a 'printed publication.'" 380 F.3d at 1352, 72 USPQ2d at 1121.<

Thus, to comply with the request for information under 37 CFR 1.105, Applicant is requested to provide:

- a copy of the poster if one was presented for the abstract at issue or a copy of the slides if slides were presented
- a statement describing all of the data that were presented and how those data are related to the data of the instant specification, even if the poster and slides are no longer available. More specifically, what were the specific changes to the HLA-E molecule, the specific point mutations, the specific regions modified and what those modifications were, and how those chimeric molecules relate to the chimeric molecules disclosed in the specification

In response to this request, Applicant is also requested to furnish:

- a statement describing additional presentations and/or abstracts presented by Applicant at scientific meetings wherein data pertinent to the subject matter was disclosed, and the contents of such disclosures, if such disclosures in fact occurred.

Note that compliance with the above requests cannot reasonably be considered burdensome since the inventors were either present at, or aware of, any disclosures of the instant claimed subject mater at scientific meetings and events prior to the filing of the instant application.

The fee and certification requirements of 37 CFR 1.97 are waived for those documents submitted in reply to this requirement. This waiver extends only to those documents within the scope of this requirement under 37 CFR 1.105 that are included in the applicant's first complete communication responding to this requirement. Any supplemental replies subsequent to the first communication responding to this requirement and any information disclosures beyond the scope of this requirement under 37 CFR 1.105 are subject to the fee and certification requirements of 37 CFR 1.97.

The Applicant is reminded that the reply to this requirement must be made with candor and good faith under 37 CFR 1.56. Where the applicant does not have or cannot readily obtain an item of required information, a statement that the item is unknown or cannot be readily obtained may be accepted as a complete reply to the requirement for that item.

This requirement is an attachment of the enclosed Office action. A complete reply to the enclosed Office action must include a complete reply to this requirement. The time period for reply to this requirement coincides with the time period for reply to the enclosed Office action.

/Ram R. Shukla/

Supervisory Patent Examiner, Art Unit 1644